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cc:

Subject: Comments on t-Butyl Alcohol

Attached please find the comments of the U.S. animal protection community on the HPV chemical test plan for t-Butyl Alcohol.

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 - t-Butyl Alcohol (PETA).pdf

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August 30, 2002

Christine Todd Whitman, Administrator
U. S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Ave., N. W.
Washington, DC 20460

Subject: Comments on the HPV Test Plan for t-Butyl Alcohol

Dear Administrator Whitman:

The following comments on the t-Butyl Alcohol High Production Volume Committee's test plan for the single chemical t-butyl alcohol (also known as t-butanol or TBA) are submitted on behalf of People for the Ethical Treatment of Animals, the Physicians Committee for Responsible Medicine, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These animal protection and environmental organizations have a combined membership of more than ten million Americans.

Overall, the test plan for t-butyl alcohol fails to recognize the breadth and depth of existing toxicity data for both humans and animals that are the result of its past extensive use and exposures. T-butyl alcohol toxicity is well studied and well understood at the screening analysis level of the HPV program. Conducting further SIDS testing on t-butyl alcohol would not change how the chemical is used or handled. Yet this test plan calls for an acute toxicity test on fish (OECD 203) and an "enhanced" combined mammalian reproductive and developmental toxicity test (OECD 421), which would kill nearly 1,000 animals.

The Committee has proposed unnecessary tests on animals and has failed to present a complete picture of the existing knowledge on t-butyl alcohol. The authors fail to explain why their proposed enhanced reproductive and developmental toxicity test is warranted under the requirements of the HPV program. They also claim that they are testing only the reproductive toxicity endpoint and not the developmental toxicity endpoint, when the expanded test they have proposed clearly examines embryonic and fetal development.

There is much available information on t-butyl alcohol, as it is a metabolite and degradation product of the well-known gasoline additive methyl t-butyl ether (MTBE). Many studies have been conducted on t-butyl alcohol. More than enough information exists to adequately characterize this chemical, and no further tests on animals can be justified. T-butyl alcohol is associated with toxicity to the central nervous system and the gastrointestinal system, liver and kidney problems, as well as minor dermal and ocular irritation. Data suggest that it is a potential carcinogen and teratogen. This chemical poses a health clear hazard to public

health and the environment and exposure should be limited to the greatest extent possible.

Additionally, the acute fish test is not necessary, as non-animal methods are available. ECOSAR, an established QSAR program that estimates toxicity to fish, invertebrates, and algae, may be appropriate for characterizing this endpoint and should be considered. The EPA encourages the use of ECOSAR in its draft guidance document *The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program* (viewable at http://www.epa.gov/chemrtk/sarfinl1.htm).

The test plan violates the following terms of the October 1999 Agreement among the EPA, industry, and environmental, health, and animal protection organizations, as well as the December 2000 *Federal Register* notice on the HPV Challenge Program:

> "In analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there is sufficient data, given the totality of what is known about a chemical, including human experience, that certain endpoints need not be tested.
>
> Participants shall maximize the use of existing and scientifically adequate data to minimize further testing.
>
> Participants shall maximize the use of scientifically appropriate categories of related chemicals and structure activity relationships."

Our main objections to this test plan are as follows:

1. The Committee fails to present comprehensive information on t-butyl alcohol.

2. The Committee fails to provide justification for its enhanced reproductive and developmental toxicity test.

3. The Committee should expand the test plan to include structurally and toxicologically similar chemicals.

1. The Committee fails to present comprehensive information on t-butyl alcohol.

The Committee claims that t-butyl alcohol is manufactured in a closed system and is used primarily for the manufacture of MTBE, a well-studied gasoline oxygenate. High purity t-butyl alcohol is also used as a solvent. The Committee contends that human exposure is unlikely, but this is highly disputable. Workers still face the risk of exposure to t-butyl alcohol in the workplace. T-butyl alcohol is also widely used in the manufacture of perfumes and a variety of cosmetics. T-butyl alcohol is also a major metabolite of MTBE in both humans and animals and is formed as a breakdown product of MTBE in air and water (Squillace, 1998). Public concern about exposure to t-butyl alcohol has increased, as t-butyl alchohol is a known drinking water contaminant, and there is potential for human exposure to t-butyl alcohol by the inhalation route

from gasoline. Exposure is also an issue of concern because tertiary alcohols are metabolized slowly and incompletely so that their toxic effects may be persistent.

Because of the adverse health effects associated with t-butyl alcohol, the Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH) have developed an eight-hour time-weighted average permissible exposure limit for t-butyl alcohol of 100 ppm (300 mg/m^3). NIOSH has a ten-hour time weighted average recommended exposure limit of 100 ppm (300 mg/m^3).

Extensive research with humans and animals has been conducted with t-butyl alcohol because of its presence in drinking water and because it is a metabolite of the well-studied gasoline additive MTBE. Vast numbers of animals have already been killed to test this substance. Yet many of these studies were not reported in this test plan's summaries. In chronic animal tests, reports on the effects on the reproductive system have not been consistent, although some adverse effects on the thyroid gland have been reported. Carcinogenicity studies with mice and rats with this material also produced equivocal results. Results of developmental toxicity studies suggest that t-butyl alcohol is associated with adverse developmental effects, although conflicting animal testing results have been published. T-butyl alcohol is also associated with toxicity to the central nervous system and the gastrointestinal system, liver and kidney problems, as well as with minor dermal and ocular irritation.

A study of the role of the t-butyl alcohol in mediating or causing the toxicity of MTBE has been conducted. A comparison of the systematic responses of the MTBE metabolites t-butyl alcohol and formaldehyde indicate that t-butyl alcohol may be partially responsible for adverse effects on the kidney, but that otherwise they are not generally responsible for toxicity associated with MTBE (Clary, 1997).

In NTP 13-week inhalation studies, rats and mice were exposed to t-butyl alcohol at concentrations of 0, 135, 270, 540, 1,080, and 2,100 ppm. Six mice died during the study and were described as having "rough coats and emaciated appearance, hypoactivity, and prostration." T-Butyl alcohol exposure appeared to be associated with organ weight changes in the kidneys and livers. In male rats, there was an exposure concentration-related increase in the severity of chronic nephropathy (NTP, 1997).

In the NTP's two-year drinking water studies with male and female rats and mice, there was some evidence of carcinogenicity of t-butyl alcohol in male F344/N rats based on renal tubule adenoma or carcinoma, but there was no evidence of carcinogenic activity in female F344/N rats. There was equivocal evidence of carcinogenicity in male mice, and some evidence of carcinogenicity in the female mice. The target organ in mice appeared to be the thyroid gland (NTP, 1995).

In a two-year drinking water study with male and female rats and mice exposed to t-butyl alcohol, the authors concluded that long-term exposure to t-butyl alcohol caused TBA "increased incidences of renal tubule adenoma and carcinoma in male rats; transitional epithelial hyperplasia of the kidney in male and female rats; follicular cell adenoma of the thyroid in female mice; and follicular cell hyperplasia of the thyroid and inflammation and hyperplasia of

the urinary bladder in male and female mice. In addition, a slight increase in follicular cell adenoma or carcinoma of the thyroid (combined) in male mice may have been related to the administration of TBA" (Cirvello et al, 1995).

In a developmental toxicity study of t-butyl alcohol in rats, the authors found that exposure via inhalation of concentrations 50 times the current permissible exposure limits for t-butyl alcohol does not produce teratogenicity in rats (Nelson, 1989). Yet conflicting results from developmental studies conducted on rats may be the result of the use of different strains of rats. When one study shows great developmental toxicity using Long-Evans rats (Abel, 1992) and another reveals low toxicity using Sprague-Dawley rats (Nelson), this strongly suggests that extrapolation of rodent results to humans in this area is virtually meaningless. With such extensive equivocal animal data already available, it is pointless to conduct additional screening level tests, which comprise the HPV program.

Human metabolism studies have been conducted. The levels of t-butyl alcohol in the blood, breath, and urine of healthy male volunteers exposed to MTBE was evaluated. T-butyl alcohol has been identified as a potential biomarker of MTBE (Johanson G, 1995).
Metabolism studies of human volunteers exposed to small concentrations of MTBE and t-butyl alcohol have been conducted (Amberg, 2001).

2. The Committee fails to provide justification for its enhanced reproductive and developmental toxicity test.

We contend that no reproductive toxicity tests are justified under the HPV program, because t-butyl alcohol has already been implicated as a hazardous chemical, and a potential carcinogen and teratogen. Logically, if a compound shows developmental toxicity and/or teratogenicity, these effects should be sufficient to prohibit or severely restrict contact with human females of reproductive age.

Even if the Committee conducts a reproductive test, it would need to provide better justification for the protocol it has proposed. The expanded reproductive and developmental toxicity test involves dosing and observing the male animals for 72 days rather than the minimum suggested by OECD TG 421 of 28 days, and the females are dosed with the chemical up to lactation day 21, rather than being killed four days after they deliver their babies. The dosing regime is comparable to the OECD TG 415 one-generation reproductive toxicity study. The Committee does not provide any justification for using this "expanded" test. The test goes above and beyond the requirements of the HPV program. The EPA must ask for a detailed explanation of why the Committee believes the traditional OECD 421 will not meet the needs of the HPV program.

We also ask that the Committee specify how many animals it intends to subject to these stressful experiments. We are concerned that this "expanded" study may also involve more animals than specified in the OECD TG 421. In the interest of animal welfare, the number of animals killed in the SIDS tests should be reduced as much as possible.

If, in fact, the Committee wishes to further explore developmental endpoints, we urge it to consider the use of an *in vitro* test for embryotoxicity (a critical endpoint in developmental toxicity) using the rodent Embryonic Stem Cell Test (EST) protocol that has been validated by the European Centre for the Validation of Alternative Methods (ECVAM). For additional information, please refer to Genschow E *et* al.: "The ECVAM international validation study on *in vitro* embryotoxicity tests: results of the definitive phase and evaluation of prediction models" *(Alternatives to Laboratory Animals* 30:
151-76, 2002). If a positive result is found, the substance should be treated as a developmental toxicant/teratogen and no further testing should be conducted under the HPV program.

3. The Committee should expand the test plan to include structurally and toxicologically similar chemicals.

T-butyl alcohol has been compared to ethanol and other alcohols in degree of toxicity. T-butyl alcohol has been found to be more toxic than ethyl, sec-butyl, and n-butyl alcohol (Gosselin, 1984). T-butyl alcohol should have been combined with the structurally related HPV chemicals butyl alcohol (CAS # 71363) and sec-butyl alcohol (CAS # 78922). These compounds are being sponsored by through the ICCA and SIDS programs.

The Committee has not drawn on the extensive body of literature on MTBE and its breakdown product t-butyl alcohol. Many animal and human studies have been conducted with t-butyl alcohol. We believe that the potential hazards of this chemical have been identified and that exposure to t-butyl alcohol should be lowered to the greatest extent possible. There is already ample information to characterize this chemical at the screening level under the HPV program and no need to subject more animals to painful, screening level tests. The EPA should require the Committee to withdraw this testing proposal and re-submit it following the use of a thoughtful toxicological analysis.

I can be reached at 757-622-7382, ext.1304, or via e-mail at jessicas@peta.org should you have any questions.

Sincerely,

Jessica Sandler, MHS
Federal Agency Liaison

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